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10/552,299	08/25/2006	Orit Kollet	30694/41506	2069

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EXAMINER	
SHEN, WU CHENG WINSTON	
ART UNIT	**PAPER NUMBER**
1632	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/552,299	KOLLET ET AL.	
	Examiner	Art Unit	
	WU-CHENG Winston SHEN	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *1* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-62* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) _____ is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☒ Claim(s) *1-62* are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Claims 1-62 are pending in the instant application. Claim 22 is a "use claims" and is interpreted as "A method of using ---". Amendments of claim 22 different from this interpretation will subject the claim to further restriction. Claims 23-29 depend from claim 22.

Election/Restrictions

2. Restriction is required under 35 U.S.C. 121 and 372.

This application contains the following inventions or groups of inventions, which are not so linked as to form a single general inventive concept under PCT Rule 13.1.

In accordance with 37 CFR 1.499, applicant is required, in reply to this action, to elect a single invention to which the claims must be restricted.

I. Claims 1-7 and 9, drawn a method of increasing sensitivity of hematopoietic stem cells *in vitro* to a chemoattractant, the method comprising exposing the stem cells to a matrix metalloprotease or an active portion thereof, which is capable of increasing a level of at least one chemoattractant receptor of the stem cells to thereby increase the sensitivity of the stem ceils to the chemoattractant.

II. Claims 1-7 and 9, drawn a method of increasing sensitivity of hematopoietic stem cells *in vivo* to a chemoattractant, the method comprising exposing the stem cells to a matrix metalloprotease or an active portion thereof, which is capable of increasing a level of at least one chemoattractant receptor of the stem cells to thereby increase the sensitivity of the stem ceils to the chemoattractant.

III. Claims 1-4, 8, and 9, drawn a method of increasing sensitivity of mesenchymal stem cells *in vitro* to a chemoattractant, the method comprising exposing the stem cells to a matrix metalloprotease or an active portion thereof, which is capable of increasing a level of at least one chemoattractant receptor of the stem cells to thereby increase the sensitivity of the stem ceils to the chemoattractant.

IV. Claims 1-4, 8, and 9, drawn a method of increasing sensitivity of mesenchymal stem cells *in vivo* to a chemoattractant, the method comprising exposing the stem cells to a matrix metalloprotease or an active portion thereof, which is capable of increasing a level of at least one chemoattractant receptor of the stem cells to thereby increase the sensitivity of the stem ceils to the chemoattractant.

V. Claims 10-16, drawn to an *in vivo* method of treating a disorder requiring cell or tissue replacement, the method comprising providing to a subject in need thereof a therapeutically effective amount of hematopoietic stem cells treated with a matrix metalloprotease or an active portion thereof, which is capable of increasing a level of at least one chemoattractant receptor of the stem cells, thereby treating the disorder requiring cell or tissue replacement in the subject.

VI. Claims 10-13 and 17, drawn to an *in vivo* method of treating a disorder requiring cell or tissue replacement, the method comprising providing to a subject in need thereof a therapeutically effective amount of mesenchymal stem cells treated with a matrix metalloprotease or an active portion thereof, which is capable of increasing a level of at least one chemoattractant receptor of the stem cells, thereby treating the disorder requiring cell or tissue replacement in the subject.

VII. Claims 18-21, drawn to a culture medium suitable for increasing the sensitivity of stem cells to a chemoattractant, the culture medium comprising a matrix metalloprotease or an active portion thereof which is capable of increasing a level of at least one chemoattractant receptor of the stem cell and a buffer solution suitable for stem cell culturing.

VIII. Claims 22-29, drawn to a method of using of a matrix metalloprotease or an active portion thereof for the manufacture of a medicament for increasing homing of stem cells to a target tissue.

IX. Claims 30-36, 38, and 39, drawn to a method of generating hematopoietic stem cells suitable for transplantation, the method comprising: (a) collecting stem cells; (b) exposing said stem cells to a matrix metalloprotease or an active portion thereof; and (c) isolating stem cells having CXCR4 levels above a predetermined threshold, to thereby generate stem cells suitable for transplantation.

X. Claims 30-33 and 37-39, drawn to a method of generating mesenchymal stem cells suitable for transplantation, the method comprising: (a) collecting stem cells; (b) exposing said stem cells to a matrix metalloprotease or an active portion thereof; and (c) isolating stem cells having CXCR4 levels above a predetermined threshold, to thereby generate stem cells suitable for transplantation.

XI. Claim 40, drawn to a method of generating hematopoietic stem cells suitable for transplantation, the method comprising: (a) collecting stem cells; (b) exposing

said stem cells to a matrix metalloprotease or an active portion thereof; and (c) isolating stem cells having CXCR4 levels above a predetermined threshold, to thereby generate stem cells suitable for transplantation, wherein collecting said stem cells is effected by: (i) a stem cell mobilization procedure; and/or (ii) a surgical procedure, the said method further comprising determining homing capabilities of said stem cells having CXCR4 levels above said predetermined threshold following step (c).

XII. Claim 40, drawn to a method of generating mesenchymal stem cells suitable for transplantation, the method comprising: (a) collecting stem cells; (b) exposing said stem cells to a matrix metalloprotease or an active portion thereof; and (c) isolating stem cells having CXCR4 levels above a predetermined threshold, to thereby generate stem cells suitable for transplantation, wherein collecting said stem cells is effected by: (i) a stem cell mobilization procedure; and/or (ii) a surgical procedure, the said method further comprising determining homing capabilities of said stem cells having CXCR4 levels above said predetermined threshold following step (c).

XIII. Claims 41, 42, 44, and 45, drawn to a nucleic acid construct comprising a first polynucleotide sequence encoding a matrix metalloportease or an active portion thereof and an inducible *cis*-acting regulatory element for directing expression of said polynucleotide in cells.

XIV. Claim 43, drawn to a nucleic acid construct comprising a first polynucleotide sequence encoding a matrix metalloportease or an active portion thereof and an

inducible *cis*-acting regulatory element for directing expression of said polynucleotide in cells, the nucleic acid further comprising a second polynucleotide sequence being translationally fused to said first polynueleotide sequence, said second polynucleotide sequence encoding a signal peptide capable of directing secretion of said matrix metalloportease or said active portion thereof out of said cells.

XV. Claim 46, drawn to a eukaryotic cell comprising a nucleic acid construct comprising a first polynucleotide sequence encoding a matrix metalloportease or an active portion thereof and an inducible *cis*-acting regulatory element for directing expression of said polynucleotide in cells.

XVI. Claim 47-52, drawn to a cell-line comprising hematopoietic stem cells transformed to express an exogenous polynucleotide encoding a matrix metalloprotease.

XVII. Claim 47-49 and 53, drawn to a cell-line comprising mesenchymal stem cells transformed to express an exogenous polynucleotide encoding a matrix metalloprotease.

XVIII. Claim 54, drawn to a method of increasing sensitivity of hematopoietic stem cells *in vitro* to a chemoattractant, the method comprising, upregulating an expression or activity of at least one endogenous MMP of the stem cells to thereby increase the sensitivity of the stem cells to the chemoattractant.

XIX. Claim 54, drawn to a method of increasing sensitivity of hematopoietic stem cells *in vivo* to a chemoattractant, the method comprising, upregulating an expression

or activity of at least one endogenous MMP of the stem cells to thereby increase the sensitivity of the stem cells to the chemoattractant.

XX. Claim 54, drawn to a method of increasing sensitivity of mesenchymal stem cells *in vitro* to a chemoattractant, the method comprising, upregulating an expression or activity of at least one endogenous MMP of the stem cells to thereby increase the sensitivity of the stem cells to the chemoattractant.

XXI. Claim 54, drawn to a method of increasing sensitivity of mesenchymal stem cells *in vivo* to a chemoattractant, the method comprising, upregulating an expression or activity of at least one endogenous MMP of the stem cells to thereby increase the sensitivity of the stem cells to the chemoattractant.

XXII. Claim 55-57, drawn to an *in vivo* method of increasing sensitivity of hematopoietic stem cell to a chemoattractant in a subject in need, the method comprising, administrating said patient with at least one matrix metalloprotease or an active portion thereof.

XXIII. Claim 55-57, drawn to an *in vivo* method of increasing sensitivity of mesenchymal stem cell to a chemoattractant in a subject in need, the method comprising, administrating said patient with at least one matrix metalloprotease or an active portion thereof.

XXIV. Claim 58, drawn to a method of generating hematopoietic stem cells suitable for transplantation, the method comprising: (a) collecting stem cells; and (b) exposing said stem cells to MMP or an active portion thereof.

XXV. Claim 58, drawn to a method of generating mesenchymal stem cells suitable for transplantation, the method comprising: (a) collecting stem cells; and (b) exposing said stem cells to MMP or an active portion thereof.

XXVI. Claim 59-62, drawn to a pharmaceutical composition comprising at least one matrix metalloprotease or an active portion thereof for treating a disorder requiring cell or tissue replacement.

3. The inventions listed as Groups I-XXVI do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons:

Applicant's claims encompass multiple inventions, multiple methods with distinct goals and methods steps (methods of increasing sensitivity of hematopoietic stem cells *in vitro* to a chemoattractant, methods of increasing sensitivity of hematopoietic stem cells *in vivo* to a chemoattractant, methods of increasing sensitivity of mesenchymal stem cells *in vitro* to a chemoattractant, methods of increasing sensitivity of mesenchymal stem cells *in vivo* to a chemoattractant, an *in vivo* method of treating a disorder requiring cell or tissue replacement, a method of using of a matrix metalloprotease or an active portion thereof for the manufacture of a medicament for increasing homing of stem cells to a target tissue, a method of generating hematopoietic stem cells suitable for transplantation, a method of generating mesenchymal stem cells suitable for transplantation etc) and multiple products (a culture medium suitable for increasing the sensitivity of stem cells to a chemoattractant, a nucleic acid construct comprising a first polynucleotide sequence encoding a matrix metalloportease or an active portion thereof and

an inducible *cis*-acting regulatory element for directing expression of said polynucleotide in cells, a eukaryotic cell comprising a nucleic acid construct comprising a first polynucleotide sequence encoding a matrix metalloportease or an active portion thereof and an inducible *cis*-acting regulatory element for directing expression of said polynucleotide in cells, a cell-line comprising hematopoietic stem cells transformed to express an exogenous polynucleotide encoding a matrix metalloprotease, a cell-line comprising mesenchymal stem cells transformed to express an exogenous polynucleotide encoding a matrix metalloprotease, a pharmaceutical composition comprising at least one matrix metalloprotease or an active portion thereof for treating a disorder requiring cell or tissue replacement), and do not have a special technical feature which link the inventions one to the other, and lack unity of invention. There is no common technical feature in Groups I-XXVI.

4. This application contains claims directed to more than one species of the generic invention. These species are deemed to lack unity of invention because they are not so linked as to form a single general inventive concept under PCT Rule 13.1.

The species are as follows:

(i) For claim 3, 12, 28, 32, 44, 48, and 56: MMP-2, MMP-3, MMP-9, MMP-10, MMP-13 and MMP-14. These are different matrix metalloproteases with different amino acid sequences rendering distinct structures and functions of the enzymes.

(ii) For claims 4, 13, 29, 33, 45, 49, 57, and 60: MMP-2 and MMP-9. These are different matrix metalloproteases with different amino acid sequences rendering distinct structures and functions of the enzymes.

(iii) For claim 21: SCF, HGF and IL-6. These are different growth factors with different structures and functions in terms of affecting the growth of cells in the culture media.

Applicant is required, in reply to this action, to elect a single species, for **(i)-(ii)** and for **(iii)**, to which the claims shall be restricted if no generic claim is finally held to be allowable. The reply must also identify the claims readable on the elected species, including any claims subsequently added. An argument that a claim is allowable or that all claims are generic is considered non-responsive unless accompanied by an election.

Upon the allowance of a generic claim, applicant will be entitled to consideration of claims to additional species which are written in dependent form or otherwise include all the limitations of an allowed generic claim as provided by 37 CFR 1.141. If claims are added after the election, applicant must indicate which are readable upon the elected species. MPEP § 809.02(a).

5. Because these inventions are independent or distinct for the reasons given above and there would be a serious burden on the examiner if restriction were not required because the inventions require a different field of search (see MPEP § 808.02), restriction for examination purposes as indicated is proper.

Applicant is advised that the reply to this requirement to be complete must include (i) an election of a species or invention to be examined even though the requirement be traversed (37 CFR 1.143) and (ii) identification of the claims encompassing the elected invention.

The election of an invention or species may be made with or without traverse. To reserve a right to petition, the election must be made with traverse. If the reply does not distinctly and specifically point out supposed errors in the restriction requirement, the election shall be treated as an election without traverse.

Should applicant traverse on the ground that the inventions or species are not patentably distinct, applicant should submit evidence or identify such evidence now of record showing the inventions or species to be obvious variants or clearly admit on the record that this is the case. In either instance, if the examiner finds one of the inventions unpatentable over the prior art, the evidence or admission may be used in a rejection under 35 U.S.C.103 (a) of the other invention.

6. Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 CFR 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a request under 37 CFR 1.48(b) and by the fee required under 37 CFR 1.17(i).

Any inquiry concerning this communication from the examiner should be directed to Wu-Cheng Winston Shen whose telephone number is (571) 272-3157 and Fax number is 571-273-3157. The examiner can normally be reached on Monday through Friday from 8:00 AM to 4:30 PM. If attempts to reach the examiner by telephone are unsuccessful, the supervisory patent examiner, Peter Paras, Jr. can be reached on (571) 272-4517. The fax number for TC 1600 is (571) 273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Wu-Cheng Winston Shen/
Patent Examiner
Art Unit 1632